

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P113001PC-Zie	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GE00/00002	International filing date (day/month/year) 28/04/2000	Priority date (day/month/year) 30/04/1999	
International Patent Classification (IPC) or national classification and IPC A61K31/00			
Applicant LOMIA, Merab			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand 30/11/2000	Date of completion of this report 02.08.2001
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EXAMINATION REPORT

International application No. PCT/GE00/00002

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):* Description, pages:

1-16 as originally filed

**Claims, No.:**

1-28 with telefax of 18/06/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

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*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*  
**see separate sheet**

## 6. Additional observations, if necessary:

### II. Priority

1.  This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
  - copy of the earlier application whose priority has been claimed.
  - translation of the earlier application whose priority has been claimed.
2.  This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

## 3. Additional observations, if necessary:

**see separate sheet**

### V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

#### 1. Statement

Novelty (N)	Yes:	Claims 3-26
	No:	Claims 1,2,27,28
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-28

Industrial applicability (IA)      Yes:      Claims 1-28  
    No:      Claims

#### 2. Citations and explanations **see separate sheet**

### VI. Certain documents cited

#### 1. Certain published documents (Rule 70.10)

and / or

#### 2. Non-written disclosures (Rule 70.9)

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**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

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**SECTION I**

1. The **amendments** filed with the telefax dated 18.06.2001 introduce subject-matter which extends beyond the content of the application as filed, contrary to Art. 34(2)(b) PCT. The amendments concerned are the following.
  - a) The formulation "...use of **anti-epileptic and anti-convulsive effective substances...**" employed in claims 1 and 27 is not clear to the IPEA, especially since the terms **anti-epileptic** and **anti-convulsive** are synonyms (Art. 6 PCT). Said formulation may be interpreted as if a **combination** of two substances was meant, for which no basis could be found in the application as originally filed. In the following procedure, it has been assumed that claims 1 and 27 are formulated in terms of the "...use of **anti-epileptic effective substances selected from the group comprising ...**", in accordance with the original application.
  - b) Item 1.a) applies mutatis mutandis to the formulation "...vigabatrin and pro gabide..." used in amended claim 13 and to the formulation "...hexamidin and primidone..." used in amended claim 15. In the following procedure, it has been assumed that said claims do not refer to combinations.
  - c) Amended claims 1 and 27 refer to the treatment of bronchial asthma "...**related diseases and syndromes...**". A basis for said amendment could not be found in the application as originally filed. The original application merely mentions a **selection** of related diseases and syndromes, e.g. asthmatic and allergic bronchitis, ..., rhinoconjunctivitis (cf. page 2, lines 10-16). In the following procedure, it has been assumed that the subject-matter of claims 1 and 27 has been restricted to **related diseases and syndromes selected from those cited in the original application**.
  - d) The original application does not contain any basis for the term "...**ester...**" used in amended claim 9.

**SECTION II**

2. A translation of the **priority document** of the present application was not available when this report was issued. In the following procedure, the IPEA has assumed that priority has been validly claimed.

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**SECTION V**

3. a) The following documents, which were cited in the International Search Report, are referred to in this report; the numbering will be adhered to in the rest of the procedure:

D1: WO 00 39091

D2: WO 99 58117

D3: WO 99 50255

D4: WO 99 43658

D5: EP 0 176 928

D6: EP 0 176 929

D7: EP 0 338 892

D8: FR 2 249 656

D9: FR 2 244 499

D10: DATABASE WPI [Online] DERWENT PUBLICATIONS LTD., LONDON, GB; AN: 1996-136303 [15]

D11: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; AN: 128:252680

D12: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; AN: 116:248319

The following document has been cited by the applicant in the description; the numbering will be adhered to in the rest of the procedure:

D13: WO 99 50225

b) D1, D2, D4 and D13: see section VI

c) D5 discloses pharmaceutical compositions comprising diazepine derivatives such as **clonazepam** which are platelet aggregation factor (PAF) antagonists (cf. page 2, lines 1-3 and page 14, compound n°3) and their use for the treatment of bronchitis, **bronchial asthma**, allergies (cf. claims 3-5).

d) D6 is a patent application of the same applicant as D5, referring to the same subject-matter as D5, except that it discloses further **diazepine derivatives**.

e) D7 refers to **benzothiazepinones** which were shown to act as calcium antagonists. They may be used as **anti-epileptics** and **anti-asthmatics** (cf. page

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13, line 33). The benzothiazepinones compounds comprise an **acetamide group** (cf. claim 1, formula I).

f) D8 discloses **thiocarbonyl oxazolidinones** which have an **anti-bronchoconstricting and anti-convulsive activity**, and are useful in the treatment of **asthma and epilepsy** (cf. page 5, lines 1-4 and claims 1, 3).

g) D9 refers to **indol-3-yl-formaldoxime carbamates** having an anti-convulsive and anti-bronchoconstricting activity (cf. claim 1 and page 5, lines 1-4). They may be used to treat **asthma and epilepsy** (cf. claim 3).

h) D10 refers to **azachroman derivatives** which are used for treating **asthma and epilepsy** (cf. abstract).

i) D11 refers to in-vivo tests wherein **carbamazepine** was shown to inhibit the **bronchoconstriction** induced by substance P, capsaicin, acetaldehyde, but not that by histamine.

4. Novelty

a) Substances comprising an **acetamide** group which may be used as anti-epileptics and anti-asthmatics are already known from D7 (cf. summary of D7: item 3.e)). Furthermore, the iminostilben derivative **carbamazepine** has already been shown to inhibit bronchoconstriction within in-vivo tests (cf. summary of D11: item 3.i)).

The subject-matter of independent **claim 1 therefore lacks novelty** over D7 and D11 (Art. 33(2) PCT).

b) Item a) applies mutatis mutandis to claims 2, 27 and 28.

c) None of the aforementioned documents discloses nor anticipates the use of the anti-epileptic substances mentioned in dependent claims 3-26, for the treatment of bronchial asthma and related diseases and syndromes selected from asthmatic and allergic bronchitis, asthmatic syndrome, bronchial hyper reactivity and bronchospastic syndromes.

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The subject-matter of dependent claims 3-26 therefore may be considered new over the cited prior art (Art. 33(2) PCT).

5. **Inventive step**

a) Document D5, which is considered to represent the most relevant state of the art, discloses (cf. item 3.c)) pharmaceutical compositions comprising diazepine derivatives such as **clonazepam** and their use for the treatment of bronchitis, **bronchial asthma**, allergies. Clonazepam is a well-known anti-convulsant drug.

The subject-matter of claims 3-26 differs from D5 in that it refers to **other anti-convulsant effective substances**, to be used for the treatment of bronchial asthma.

The problem to be solved may therefore be regarded as to provide an **alternative anti-epileptic drug** for the treatment of bronchial asthma.

As already mentioned before, D6, D7, D8, D9, D10 and D11 already disclose various substances having anti-epileptic as well as anti-asthmatic effects.

For the skilled man, it is therefore easily derivable from D5, alone or in combination with any of the aforementioned documents, that anti-epileptic drugs in general, such as the compounds mentioned in claims 3-26, may be useful in the treatment of bronchial asthma.

Thus, **the subject-matter of claims 3-26 appears to lack an inventive step** (Art. 33(3) PCT).

It is pointed out, that even if an inventive step was acknowledged for some of said claims, a unity problem may arise (Rule 13.1 PCT). Indeed, since the use of the anti-epileptic drug clonazepam for the treatment of asthma is already known from the prior art, there appears to be no single general inventive concept linking together the anti-epileptic drugs enumerated in the present application.

**SECTION VI**

6. a) Certain published documents (Rule 70.10)

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Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 0039091 (D1)	06.07.00	01.12.99	29.12.98
WO 9958117 (D2)	18.11.99	06.05.99	13.05.98
WO 9943658 (D4)	02.09.99	20.11.98	27.02.98
WO 9950225 (D13)	07.10.99	01.04.99	05.02.99, 01.04.98

b) D1 refers to **3,3-biarylpiridine and 2,2-biarylmorpholine derivatives** that are selective delta opioid ligands and may be used to treat **epilepsy** and respiratory disorders such as **asthma** (cf. page 2, line 32 to page 3, line 8).

c) D2 refers to the use of ligands for benzodiazepine peripheral receptors, such as **clonazepam**, in compositions to inhibit apoptosis (cf. claim 1 and drawing 1/1). They may be used to treat **asthma** (cf. claim 5).

d) D4 refers to **heterocyclic substituted aniline calcium channel blockers** which may be used to treat **asthma** and **epilepsy** (cf. page 1, lines 4-7 and claims 1, 35, 36).

e) D13 refers to **aminocyclohexylether compounds** and their use for the treatment of **epilepsy**, respiratory disorders and **asthma** in warm-blooded animals (cf. page 1, lines 3-5 and claims 18-21, 26-27, 30-31).

## **SECTION VIII**

7. The description refers to diseases which are not linked to **asthma** (cf. pages 12-13) (Art. 6 PCT).
8. The Applicant is informed that the formulation "...remacimide, hydrochloride, ..." used in claim 27 was assumed to be remacemide hydrochloride (Art. 6 PCT).
9. Item 8. also applies to the term "...pirazol..." used in claim 1 and in the description which was assumed to be pyrazol (Art. 6 PCT).

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CLAIMS

- 1) Use of antiepileptic agents, their derivates and analogues, their tautomers and pharmaceutically acceptable compounds comprising:
  - a) blocking induction of epileptic activity on endoneuronal level inhibiting "sudden" pacemaker activity and action of any epileptogenic factors and agents, and/or
  - 5 b) affecting both an occurrence and dissemination of epileptogenic activity by suppressing pacemaker potentials, action potential of synaptic membrane, synaptic transmission by inhibiting sodium-dependent and/or other exciting postsynaptic potentials, and/or
  - c) impeding dissemination, generalization of epileptic activity and affecting mainly the synaptic formations, increasing brain inhibitory systems or decreasing brain excitation systems,
  - 10 d) correcting, modulating and/or inhibiting paroxysmal descending impulses to respiratory ways from the central nervous system and paroxysmal activity induced in bronchial smooth muscles and/or induced therein, and/or
  - e) acting otherwise as medical means for treatment of all types of bronchial asthma, asthmatic
  - 15 status, asthmatic and allergic bronchitis, asthmatic syndrome, bronchial hyperreactivity and bronchospastic syndromes, and for treatment of diseases and pathological conditions proceeding with these syndromes and also allergic and vasomotor rhinitis and rhinoconjunctivitis.
- 2) Usage of various antiepileptic agents from various chemical groups, according to item 1: derivates, analogues, tautomers and pharmaceutically acceptable compounds of 1) barbituric acid, 2) hydantoin (e.g. phenytoin, fosphenytoin), 3) pyrimidine (e.g. hexamidin, primidone), 4) oxazolidinedione (e.g. trimethindione), 5) indandione (e.g. methindion), 6) succinimide (e.g. aethosuximide), 7) iminostilben (e.g. carbamazepine, oxcarbazepine), 8) butamsultham (e.g. sultiam), 9) 1,4 benzodiazepines (e.g. clonazepam), 10) 1,5 benzodiazepines (e.g. clobazam), 11) valproic acid and salts of valproic acid, 12) aminoindandions (e.g. methindione), 13) 25 acetylcarbamate (e.g. phenacetamide), 14) beta-chlorpropionic acid (e.g. beclamide), 15) tетronic acid (e.g. losigamone), 16) sulfonamides (e.g. zonisamide), 17) fructose sulfamates (e.g. topiramate), 18) pyrrolidine (e.g. levetiracetam), 19) acetamides (e.g. remacemide hydrochloride), 20) propylene glycols (e.g. felbamate), 21) nipecotic acid (e.g. tiagabine), 22) triasines (e.g. lamotrigine), 23) gamma-aminobutyric acid (e.g. vigabatrin, gabapentin, progabide), 24) thiazoles (e.g. ralitoline) 25) selenazoles, 26) pirazoles, 27) izatine, 28) diphenylsulphone, 29) ethylselenazolidindione, 30) benzimidazolin-2tione, 31) dioxolanes (e.g. stiripentol), 32) azetidines (e.g. dezinamide), 33) triazoles (e.g. loreclezole), 34) acetamides (e.g. milacemide), 35) imidazoles (e.g. nafimidone), and other antiepileptic agents.